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Comparative efficacy of eight oral Chinese patent medicines for dilated cardiomyopathy with heart failure: a Bayesian network meta-analysis

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Abstract

Background Chinese patent medicines (CPMs) are widely used in China as an adjuvant treatment in dilated cardiomyopathy with heart failure (DCM-HF). However, comprehensive and systematic evidence supporting the beneficial effects of CPMs combined with current complementary and alternative medicine (CAM) treatments against DCM-HF was limited. This network meta-analysis (NMA) aimed to assess and rank the relative efficacy of eight different CPMs for DCM-HF.

Methods To retrieve randomized controlled trials (RCTs) focusing on the use of CPMs combined with CAM for DCM-HF, the databases of PubMed, Embase, Web of Science Core Collection, Cochrane Library, ProQuest, China National Knowledge Infrastructure (CNKI), China Science Periodical Database (CSPD), Chinese Citation Database (CCD), Chinese Biomedical Literature Database (CBM), and ClinicalTrials.gov were comprehensively searched from their inception to 29 February 2024. The quality of the included RCTs was examined using the Cochrane Risk of Bias assessment tool, version 2.0 (RoB 2). Surface under the cumulative ranking curve (SUCRA) probability values were applied to rank the relative efficacy. Bayesian network meta-analysis was designed to assess the efficacy of different CPMs.

Results After applying the inclusion and exclusion criteria, a total of 77 eligible RCTs involving 6980 patients were enrolled. The outcomes assessed included clinical effectiveness rate (CER), left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), 6-min walk test (6MWT), brain natriuretic peptide (BNP), and cardiac output (CO). The results of the NMA indicated that Qili Qiangxin capsule (QLQX), Wenxin granule (WX), Tongxinluo capsule (TXL), Qishen Yiqi dropping pill (QSYQ), Shexiang Baoxin pill (SXBX), Yangxinshi tablet (YXST), Yixinshu capsule (YXSC), and Getong Tongluo capsule (GTTL) combined with CAM significantly improved performance compared with CAM alone in treating DCM-HF. YXST + CAM (MD = −9.93, 95% CI −12.83 to −7.03) had the highest probability of being the best treatment on account of the enhancement of LVEF. WX + CAM had the highest likelihood of being the best treatment considering the improvement in LVEDD (MD = −11.7, 95% CI −15.70 to −7.79) and 6MWT (MD = −51.58, 95% CI −73.40 to −29.76). QLQX + CAM (MD = −158.59, 95% CI −267.70 to −49.49) had the highest likelihood of being the best intervention for the reduction in BNP. TXL + CAM (MD = −0.93, 95% CI −1.46 to −0.40) might

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be the optimal choice for increasing CO levels in DCM-HF patients. No serious treatment-emergent adverse events were observed.

Conclusion This NMA suggested that adding CPMs to the current CAM treatment exerted a more positive effect on DCM-HF. Thereinto, QLQX + CAM, TXL + CAM, WX + CAM, and YXST + CAM showed a preferable improvement in patients with DCM-HF when unified considering the clinical effectiveness rate and other outcomes. Furthermore, due to the lack of information on CPMs against DCM-HF and the uneven distribution of included studies among interventions, more high-quality studies are needed to provide more robust evidence to support our findings.

Systematic review registration PROSPERO (CRD42023482669).

Keywords Chinese patent medicine, Dilated cardiomyopathy, Heart failure, Network meta-analysis, Traditional Chinese medicine

Introduction

Dilated cardiomyopathy (DCM) is a heterogeneous group characterized by the presence of left ventricular dilatation and contractile dysfunction, in the absence of abnormal loading conditions and severe coronary artery disease [1, 2]. It is generally considered to be the ultimate response of the cardiac muscle to genetically and environmentally acquired injuries [3, 4]. According to the Global Burden of Disease survey in 2015 [5], the prevalence of cardiomyopathy across the globe was estimated to be 2.5 million instances, representing a rise of 27% in just 10 years. Data from a large retrospective study which included 9 million individuals showed that there were approximately 4.3 cases of DCM per 10,000 people [6]. DCM poses a serious threat and burden to patients' lives due to heart failure (HF), arrhythmia, thromboembolic events, and sudden death. Of concern, HF caused by DCM is the most important cause of death [2, 7].

For patients with established DCM, treatment is directed at the major clinical manifestations of HF and arrhythmias. Prevention and treatment of thromboembolism might also be required [2]. Clinical therapies such as pharmacological and non-pharmacological treatment, electrical device therapies, surgery, heart transplantation, and mechanical support are determined according to the stage and severity of the disease [2, 8]. Nevertheless, historic survival data indicated that adult patients with DCM have a poor prognosis, with a 1-year mortality of 25–30% and a 50% survival at 5 years [9]. Thus, it is highly required to seek out potential adjuvant and alternative treatments for this significant medical need.

The growing application of current complementary and alternative medicine (CAM) treatments in treating DCM has received widespread attention in recent years. In China, oral traditional Chinese patent medicines (CPMs) are extensively used as an adjuvant therapy for DCM-HF. A conventional meta-analysis of 3334 patients revealed that combining CPMs with current CAM treatments had beneficial effects against DCM-HF [10]. However, clinical trials assessing CPMs combined with CAM in the treatment of DCM-HF were still insufficient, and comprehensive and systematic evidence supporting the beneficial effects of different types of CPMs combined with CAM against DCM-HF has not been reported. Compared with conventional meta-analyses, network meta-analyses (NMA) could combine evidence from direct and indirect comparisons to identify the optimal therapeutic regimen, contributing to evidence-based medical evidence for drug selection in clinical decision-making [11, 12].

Therefore, eight most commonly used CPMs for the treatment of DCM-HF were examined (Table 1), namely Qili Qiangxin capsule (QLQX), Wenxin granule (WX), Tongxinluo capsule (TXL), Qishen Yiqi dropping pill (QSYQ), Shexiang Baoxin pill (SXBX), Yangxinshi tablet (YXST), Yixinshu capsule (YXSC), and Getong Tongluo capsule (GTTL). A NMA of randomized controlled trials (RCTs) was performed to comprehensively evaluate and rank the relative potentiality for DCM-HF of CPMs among all available publications.

Materials and methods

This NMA was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension Statement [13]. A completed PRISMA checklist was included as an additional file (Additional file 1: Table S1). The protocol for the current review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42023482669.

Search strategy

The literature search was carried out in PubMed, Embase, Web of Science Core Collection, Cochrane Library, ProQuest, China National Knowledge Infrastructure (CNKI), China Science Periodical Database (CSPD), Chinese Citation Database (CCD), Chinese Biomedical Literature Database (CBM), and ClinicalTrials.gov from

Table 1 Details of eight Chinese patent medicines

Chinese patent medicine	Chinese name	Latin name	Species	Family
Qili Qiangxin capsule	Huangqi	Astragali Radix	*Astragalus membranaceus* (Fisch.) Bge	Fabaceae
	Renshen	Ginseng Radix et Rhizoma	*Panax ginseng* C.A.Mey	Araliaceae
	Fuzi	Aconiti Lateralis Radix Praeparata	*Aconitum carmichaeli* Debx	Ranunculaceae
	Danshen	Salviae Miltiorrhizae Radix et Rhizoma	*Salvia miltiorrhiza* Bge	Lamiaceae
	Tinglizi	Descurainiae Semen, Lepidii Semen	*Descurainia Sophia* (L.) Webb. et Prantl	Cruciferae
	Zexie	Alismatis Rhizoma	*Alisma orientalis* (Sam.) Juzep	Alismaceae
	Yuzhu	Polygonati Odorati Rhizoma	*Polygonatum odoratum* (Mill.) Druce	Liliaceae
	Guizhi	Cinnamomi Ramulus	*Cinnamomum cassia* Presl	Lauraceae
	Honghua	Carthami Flos	*Carthamus tinctorius* L	Asteraceae
	Xiangjiapi	Periplocae Cortex	*Periploca sepium* Bge	Asclepiadaceae
	Chenpi	Citri Reticulatae Pericarpium	*Citrus reticulata* Blanco	Rutaceae
Wenxin granule	Dangshen	Codonopsis Radix	*Codonopsis pilosula* (Franch.) Nannf	Campanulaceae
	Huangjing	Polygonati Rhizoma	*Polygonatum sibiricum* Red	Liliaceae
	Sanqi	Notoginseng Radix et Rhizoma	*Panax notoginseng* (Burk.) F. H. Chen	Araliaceae
	Hupo	Succinum	-	-
	Gansong	Nardostachyos Radix et Rhizoma	*Nardostachys jatamansi* DC	Valerianaceae
Tongxinluo capsule	Renshen	Ginseng Radix et Rhizoma	*Panax ginseng* C.A.Mey	Araliaceae
	Shuizhi	Hirudo	*Whitmania pigra* Whitman	Hirudinidae
	Quanxie	Scorpio	*Buthus martensii* Karsch	Buthidae
	Chishao	Paeoniae Radix Rubra	*Paeonia lactiflora* Pall	Ranunculaceae
	Chantui	Cicadae Periostracum	*Cryptotympana pustulata* Fabricius	Cicadidae
	Tubiechong	Eupolyphaga Steleophaga	*Eupolyphaga sinensis* Walker	Corydiidae
	Wugong	Scolopendra	*Scolopendra subspinipes mutilans* L. Koch	Scolopendridae
	Tanxiang	Santali Albi Lignum	*Santalum album* L	Santalaceae
	Jiangxiang	Dalbergiae Odoriferae Lignum	*Dalbergia odorifera* T. Chen	Fabaceae
	Ruxiang	Olibanum	*Boswellia carterii* Birdw	Buseraceae
	Suanzaoren	Ziziphi Spinosae Semen	*Ziziphus jujuba* Mill. var. spinosa (Bunge) Hu ex H. F. Chou	Rhamnaceae
	Bingpian	Borneolum	*Cinnamomum camphora* (L.) Presl	Lauraceae
Qishen Yiqi dropping pill	Huangqi	Astragali Radix	*Astragalus membranaceus* (Fisch.) Bge	Fabaceae
	Danshen	Salviae Miltiorrhizae Radix et Rhizoma	*Salvia miltiorrhiza* Bge	Lamiaceae
	Sanqi	Notoginseng Radix	*Panax notoginseng* (Burk.) F. H. Chen	Araliaceae
	Jiangxiang	Dalbergiae Odoriferae Lignum	*Dalbergia odorifera* T. Chen	Fabaceae
Shexiang Baoxin pill	Shexiang	Moschus	*Moschus berezovskii* Flerov	Cervidae
	Renshen	Ginseng Radix et Rhizoma	*Panax ginseng* C.A.Mey	Araliaceae
	Niuhuang	Bovis Calculus	*Bos taurus domesticus* Gmelin	Bovidae
	Rougui	Cinnamomi Cortex	*Cinnamomum cassia* Presl	Lauraceae
	Suhexiang	Styrax	*Liquidambar orientalis* Mill	Hamamelidaceae
	Chansu	Bufonis Venenum	*Bufo bufo gargarizans* Cantor	Bufonidae
	Bingpian	Borneolum	*Cinnamomum camphora* (L.) Presl	Lauraceae

Table 1 (continued)

Chinese patent medicine	Chinese name	Latin name	Species	Family
Yangxinshi tablet	Huangqi	Astragali Radix	*Astragalus membranaceus* (Fisch.) Bge	Fabaceae
	Dangshen	Codonopsis Radix	*Codonopsis pilosula* (Franch.) Nannf	Campanulaceae
	Danshen	Salviae Miltiorrhizae Radix et Rhizoma	*Salvia miltiorrhiza* Bge	Lamiaceae
	Gegen	Puerariae Lobatae Radix	*Pueraria lobata* (Willd.) Ohwi	Fabaceae
	Yinyanghuo	Epimedii Folium	*Epimedium brevicornum* Maxim	Berberidaceae
	Shanzha	Crataegi Fructus	*Crataegus pinnatifida* Bge. var. major N. E. Br	Rosaceae
	Dihuang	Rehmanniae Radix	*Rehmannia glutinosa* Libosch	Scrophulariaceae
	Danggui	Angelicae Sinensis Radix	*Angelica sinensis* (Oliv.) Diels	Umbelliferae
	Huanglian	Coptidis Rhizoma	*Coptis chinensis* Franch	Ranunculaceae
	Yanhusuo	Corydalis Rhizoma	*Corydalis yanhusuo* W. T. Wang	Papaveraceae
	Lingzhi	Ganoderma	*Ganoderma lucidum* (Leyss.ex Fr.) Karst	Polyporaceae
	Renshen	Ginseng Radix et Rhizoma	*Panax ginseng* C.A.Mey	Araliaceae
	Gancao	Glycyrrhizae Radix et Rhizoma	*Glycyrrhiza uralensis* Fisch	Fabaceae
Yixinshu capsule	Renshen	Ginseng Radix et Rhizoma	*Panax ginseng* C.A.Mey	Araliaceae
	Maidong	Ophiopogonis Radix	*Ophiopogon japonicus* (L.f) Ker-Gawl	Liliaceae
	Wuweizi	Schisandrae Chinensis Fructus	Schisandra Chinensis (Turcz.) Baill	Magnoliaceae
	Huangqi	Astragali Radix	*Astragalus membranaceus* (Fisch.) Bge	Fabaceae
	Danshen	Salviae Miltiorrhizae Radix et Rhizoma	*Salvia miltiorrhiza* Bge	Lamiaceae
	Chuanxiong	Chuanxiong Rhizoma	*Ligusticum chuanxiong* Hort	Umbelliferae
	Shanzha	Crataegi Fructus	*Crataegus pinnatifida* Bge. var. major N. E. Br	Rosaceae
Getong Tongluo capsule	Gegen	Puerariae Lobatae Radix	*Pueraria lobata* (Willd.) Ohwi	Fabaceae

their inception to 29 February 2024 by two researchers independently for ongoing and unpublished trials and potential trials (Additional file 2). Search terms and MeSH headings were related to combinations of "Chinese patent medicine" and "dilated cardiomyopathy", and our search strategy was tailored for each database. Furthermore, related reference studies were manually retrieved from the databases, and relevant systematic reviews and guideline references were also considered.

Study selection

Studies were considered eligible for inclusion if the following criteria were met: (1) the study was an RCT with no limitations on language, publication year, publication status, or the use of blinding methods. (2) Patients enrolled in the RCTs were diagnosed with DCM, which could be based on the current or past diagnostic criteria. But the criteria must at least meet the definition of DCM in the "1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies" [14]: (1) impaired dilatation and contraction of the left ventricle or both ventricles; (2) the degree of myocardial dysfunction is not explained by the abnormal loading conditions or the extent of ischemic damage; (3) histology is nonspecific; (4) presentation is usually with heart failure, which is often progressive; and (5) the absence of hypertension, valvular heart disease, congenital heart disease, and ischemic heart disease at the time of onset. The participants were definitely diagnosed with HF according to the 2023 European Society of Cardiology (ESC) Guidelines for HF [15]. Additionally, their cardiac function was consistent with grades II to IV of the New York Heart Association (NYHA) classification [16]: the patient's physical activity ranged from mild limitation to inability to engage in any physical activity. We imposed no limitations on gender, nationality, or ethnic origin. (3) Patients in the experimental group received one of the eight CPMs (QLQX, WX, TXL, QSYQ, SXBX, YXST, YXSC, and GTTL) along with the current CAM treatments for DCM-HF, while the control group received CAM alone. There were no restrictions on the dosage, timing, or duration of administration for the CPMs' use. (4) The primary outcome was clinical effectiveness rate (CER), and the secondary outcomes were left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), 6-min walk test (6MWT), brain natriuretic peptide (BNP), and cardiac output (CO). Studies that did

not include any of the above outcomes were excluded. In addition, treatment-emergent adverse events will also be recorded and analyzed in this work. The therapeutic effect standard referred to the following definitions: (1) markedly effective: the improvement of NYHA was more than two grades, and there was an obvious improvement in the clinical symptom. (2) effective: the improvement of NYHA was more than one grade, and the clinical symptom improved partly. (3) ineffective: it did not reach the above standards of efficiency, and even exacerbation. CER = markedly effective rate + effective rate.

Studies were excluded if any of the following criteria were met: (1) The cause of HF in patients in RCTs was not due to DCM. (2) The sample size of RCTs was less than 30. (3) The intervention was a combination of multiple therapies or did not specify a therapeutic agent. (4) In cases where a study was republished, only versions with larger sample sizes and more comprehensive data would be retained. (5) A lack of complete or precise data or the full text was not available.

Data extraction

EndNote 20 software was used for the management of the literature from different databases. Two researchers (ST and LY) independently screened the literature according to the inclusion criteria. After checking for duplicate studies, the researchers eliminated irrelevant literature by browsing the titles and abstracts. Finally, the full text was read to select eligible studies. Information from the eligible RCTs was extracted by the two researchers independently based on a custom-made form. The recorded information consisted of the following items: the first author, publication year, gender composition, average ages, sample sizes, cardiac function classification, randomization and blinding method, intervening measure, control measures, course of treatment, dosages of drugs, outcome data, information about quality assessment of RCTs. Any disagreement was resolved by discussion or a third researcher (JL).

Quality assessment

The quality assessment was independently evaluated by two reviewers (ST and LY) with the Cochrane Risk of Bias assessment tool, version 2.0 (RoB 2). The quality assessment items of Cochrane tools included the following: (1) selection bias: random sequence generation and allocation concealment; (2) performance bias: blinding of the participants and personnel; (3) detection bias: blinding of the outcome assessment; (4) attrition bias: incomplete outcome data; (5) reporting bias: selective reporting; and (6) other bias. Bias in each aspect was evaluated as "low risk," "unclear," and "high risk." Any existing disagreements were discussed or consulted with the third researcher (JL).

Grading of the evidence

The GRADE approach was used to assess the certainty of the evidence [17]. The certainty of the evidence was graded as high, moderate, low, or very low. RCT trials receive an initial grade of high by default and are downgraded based on the following pre-specified criteria: risk of bias (the included studies were biased in randomization, allocation concealment and blinding), inconsistency (the overlapping degree of confidence intervals of different studies was poor, and the I^2 value of the combined results was > 50%), indirectness (presence of factors that limit the generalizability of the results), imprecision (the sample size of included studies was small and the confidence interval was wide), and other considerations.

Statistical analysis

The NMA was performed by using Stata software (version 16) and Review Manager software (version 5.4). For dichotomous outcomes, the combined results were calculated as risk ratios (RRs). For continuous outcomes, the mean and the standard deviation of the change amount were calculated according to the pre- and post-treatment, and the mean difference (MD) was used as the effect analysis statistic. The effect sizes were expressed as 95% confidence intervals (95% CIs). When the 95% CIs of the RRs did not include one and the 95% CIs of the MD did not include zero, the differences between the groups were considered statistically significant. The network graph of the indirect comparative relationship between different interventions was developed using Stata software. Provided that the closed loop of interventions was available, a loop-specific approach was explored to examine the inconsistency of evidence. Surface under the cumulative ranking curve (SUCRA) probability values were applied to rank the interventions, and SUCRA values of 100% and 0% were assigned to the best and worst treatments. Necessary subgroup analyses were conducted on eligible studies based on drug dosage, treatment duration, and age of administration to further explore potential heterogeneity. Forest and funnel plots of outcome indicators were developed using Stata software to visualize the comparison results and test the publication bias.

Results

Search results

Overall, a total of 812 studies were identified in the initial search (Fig. 1). After removing duplicates, 569 studies were retained. After screening titles and abstracts, 435 studies were excluded because of irrelevant study design.

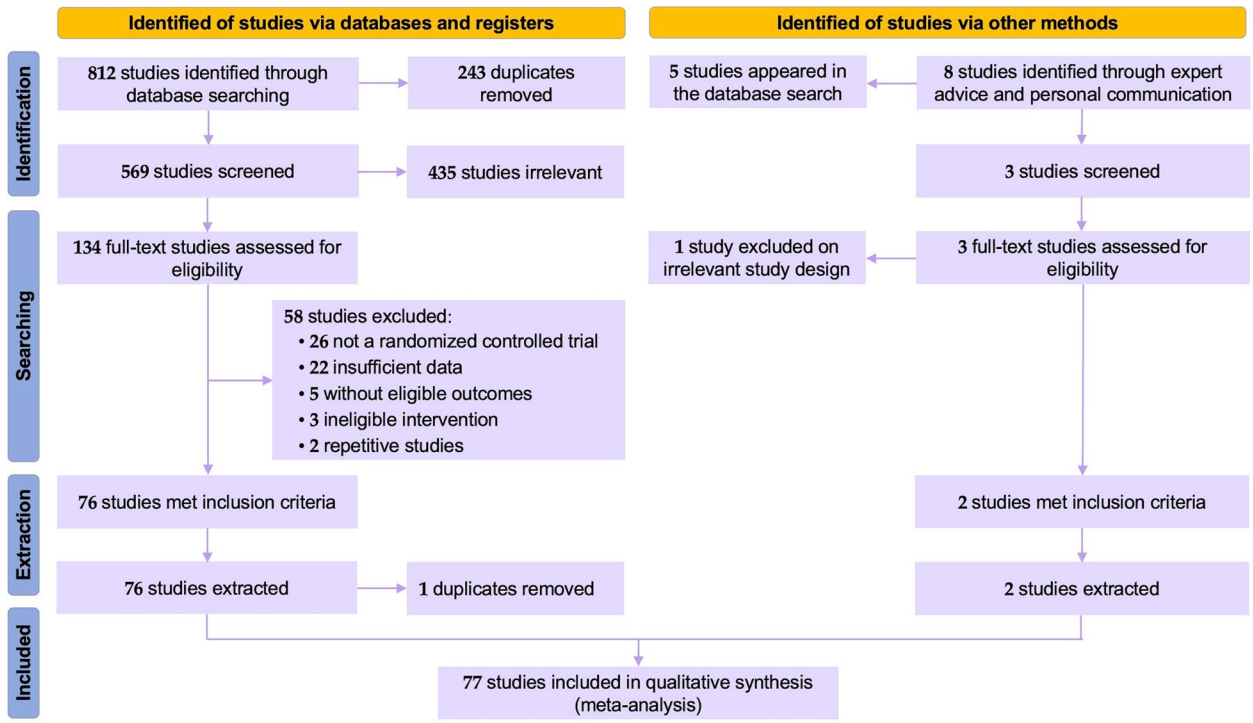

Fig. 1 Flow chart of the search for eligible studies

Afterward, 134 studies were eligible and examined, of which 58 were further excluded due to the following reasons: (1) the study type missed eligibility criteria ($n=26$), (2) studies with insufficient data ($n=22$), (3) studies without eligible outcomes ($n=5$), (4) the study's intervention missed eligibility criteria ($n=3$), and (5) repetitive studies ($n=2$). Furthermore, 8 studies were identified through expert advice and personal communication and 6 studies were excluded because they were irrelevant and animal experiment reports.

Finally, 77 eligible RCTs that evaluated the use of 8 CPMs combined with CAM against DCM-HF were included for the NMA, including QLQX (47 RCTs), WX (11 RCTs), TXL (8 RCTs), QSYQ (2 RCTs), SXBX (3 RCTs), YXST (2 RCTs), YXSC (2 RCTs), and GTTL (2 RCTs); all of them were carried out in China between 2006 and 2023.

Study characteristics

Seventy-seven RCTs with 6980 patients accorded with the eligibility criteria, including 3523 patients in the experimental groups and 3457 patients in the control groups [18–94]. Among the participants, more than half were men and the majority were middle-aged and elderly people. The intervention in the control groups was current CAM treatments, including angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists, cardiac glycosides, nitrates, beta-blockers, and so on. The experimental groups received one of the CPMs identified based on the control groups. The duration of RCTs ranged from 1 to 48 weeks; it was 12 weeks in 33.8% of RCTs and 4 weeks in 27.3% of them, respectively. The details of the study characteristics are presented in Table 2.

The compared connections among interventions for each outcome are shown in Fig. 2. Each node represents a different intervention and the size of nodes is positively correlated with the number of patients. The thickness of the line segment corresponds to the number of included studies for that intervention. The thicker the line segment, the larger the number of included studies for that intervention is. There were no closed loops formed between the studies, thus, the assumption of consistency between direct and indirect evidence was not utilized in this NMA.

Quality evaluation

The Cochrane risk-of-bias assessment tool was used to perform a quality evaluation. Thirty-one studies generated randomization via random number table [24, 25, 33, 34, 37, 39, 41, 42, 44, 46–49, 52–55, 57, 60, 62, 63, 66, 72, 75, 78–80, 82–84, 94], and two studies generated randomization via draw method [38, 51]. Besides, block randomization, stratified randomization, touch ball method,

Table 2 Characteristics of the included studies

Study ID	*N* (E/C)	Male/female		Age (years)		NYHA (I, II, III, IV)		Intervention		Duration (week)	Outcomes
		E	C	E	C	E	C	E	C		
Zhao et al. 2009 [18]	34/34	23/11	21/13	–		0, 14, 20, 0	0, 15, 19, 0	QLQX + CAM	CAM	4	①
Liu et al. 2009 [19]	21/20	13/8	12/8	41 ± 11	40 ± 10	0, 12, 9, 0	0, 12, 8, 0	QLQX + CAM	CAM	24	①②③④⑤
Zhu et al. 2010 [20]	40/40	–		52.3 ± 14.2		0, 20, 29, 31		QLQX + CAM	CAM	12	②③
Lin, 2010 [21]	30/30	15/15	12/18	40 ± 13	38 ± 12	–		QLQX + CAM	CAM	24	①②③④⑤
Yuan, 2012 [22]	30/32	20/10	16/16	41.65 ± 9.33	43.08 ± 7.5	0, 0, 12, 18	0, 0, 16, 16	QLQX + CAM	CAM	4	②③④
Zhao et al. 2012 [23]	34/34	21/13	23/11	–		0, 14, 20, 0	0, 15, 19, 0	QLQX + CAM	CAM	4	②④⑤
Yang et al. 2013 [24]	34/34	21/13	19/15	53.8 ± 10.1	54.6 ± 10.8	–		QLQX + CAM	CAM	12	②③⑥
Yu, 2013 [25]	32/32	19/13	20/12	59 ± 12	61 ± 12	–		QLQX + CAM	CAM	4	②③④⑤
Zhang et al. 2013 [26]	35/35	42/28		–		0, 0, 60, 10		QLQX + CAM	CAM	8	①②③⑤
Yi et al. 2014 [27]	45/45	25/20	26/19	52.4 ± 12.7	53.1 ± 13.4	0, 16, 18, 11	0, 14, 19, 12	QLQX + CAM	CAM	4	②③⑤
Wu et al. 2014 [28]	24/24	18/6	17/7	52.6 ± 10.7	53.9 ± 9.3	0, 9, 15, 0	0, 8, 16, 0	QLQX + CAM	CAM	12	②④
Zhou et al. 2015 [29]	20/24	13/7	12/12	46.45 ± 28.29	47.38 ± 25.46	0, 11, 9, 0	0, 13, 11, 0	QLQX + CAM	CAM	24	②③
Fu et al. 2016 [30]	30/30	22/8	23/7	56.6 ± 18.8	58.4 ± 19.3	0, 12, 18, 0	0, 10, 20, 0	QLQX + CAM	CAM	4	①②③
Ma et al. 2016 [31]	31/32	34/29		–		–		QLQX + CAM	CAM	24	①②
Wu et al. 2016 [32]	30/30	19/11	20/10	56.7 ± 7.8	57.3 ± 7.1	0, 5, 13, 12	0, 6, 14, 10	QLQX + CAM	CAM	12	②④⑤
Leng, 2016 [33]	31/31	21/10	16/15	54.65 ± 9.33	55.19 ± 7.55	0, 0, 12, 19	0, 0, 13, 18	QLQX + CAM	CAM	4	②③④⑤
Jing et al. 2017 [34]	43/42	21/22	19/23	41.3 ± 10.1	41.1 ± 9.8	–		QLQX + CAM	CAM	2	①②③④⑤
Wu et al. 2018 [35]	278/278	139/139	158/120	49.94 ± 21.58	53.19 ± 19.57	0, 165, 113, 0	0, 184, 94, 0	QLQX + CAM	CAM	48	②③
Zhao, 2018 [36]	40/40	24/16	26/14	61.5 ± 12.3	62.2 ± 12.6	0, 13, 18, 9	0, 12, 18, 10	QLQX + CAM	CAM	4	②③④⑤
Yao, 2018 [37]	48/48	30/18	29/19	54.60 ± 5.61	55.21 ± 4.68	–		QLQX + CAM	CAM	4	①
Huang, 2018 [38]	30/30	19/11	18/12	52.1 ± 3.2	52.2 ± 3.4	0, 0, 21, 9	0, 0, 20, 10	QLQX + CAM	CAM	4	①②
Wang et al. 2019 [39]	68/68	35/33	38/30	67.98 ± 6.03	68.54 ± 6.12	0, 24, 44, 0	0, 26, 42, 0	QLQX + CAM	CAM	4	①②⑤
Ren et al. 2019 [40]	64/64	34/30	32/32	71.4 ± 6.2	70.3 ± 5.8	–		QLQX + CAM	CAM	2	①②③
Liu et al. 2019 [41]	41/41	18/23	19/22	41.41 ± 5.35	41.39 ± 5.32	–		QLQX + CAM	CAM	2	①②③⑤
Zheng et al. 2019 [42]	52/52	29/23	28/24	42.14 ± 7.62	41.95 ± 7.84	0, 7, 29, 16	0, 5, 30, 17	QLQX + CAM	CAM	2	①②③
Dong, 2019 [43]	40/39	26/14	25/14	53.7 ± 10.6	54.9 ± 11.2	0, 14, 18, 8	0, 13, 19, 7	QLQX + CAM	CAM	2	①②③④
Yang et al. 2019 [44]	60/58	35/25	33/25	49.14 ± 13.52	47.89 ± 12.83	0, 23, 22, 15	0, 21, 24, 13	QLQX + CAM	CAM	24	②③
Dai et al. 2019 [45]	48/47	25/23	25/22	37.72 ± 3.85	37.86 ± 3.71	0, 0, 24, 24	0, 0, 23, 24	QLQX + CAM	CAM	12	①②
Shi, 2020 [46]	30/30	16/14	17/13	65.5 ± 3.4	65.4 ± 3.6	0, 10, 20, 0	0, 11, 19, 0	QLQX + CAM	CAM	4	①②
Li et al. 2020 [47]	40/40	27/13	26/14	54.58 ± 9.23	54.74 ± 9.36	0, 11, 19, 10	0, 12, 17, 11	QLQX + CAM	CAM	4	②③
Niu et al. 2020 [48]	68/67	42/26	41/26	47.05 ± 5.01	46.75 ± 5.012	0, 29, 24, 15	0, 30, 23, 14	QLQX + CAM	CAM	4	①②④
Yao et al. 2020 [49]	48/48	25/23	28/20	50.43 ± 6.24	50.53 ± 6.12	0, 24, 18, 6	0, 27, 16, 5	QLQX + CAM	CAM	12	①②③⑥
Li, 2020 [50]	30/30	21/9	22/8	65.78 ± 2.21	65.89 ± 2.46	–		QLQX + CAM	CAM	2	①
Meng, 2020 [51]	50/50	27/23	26/24	58.19 ± 3.25	58.25 ± 3.67	–		QLQX + CAM	CAM	2	①②③④⑤

Table 2 (continued)

Study ID	*N* (E/C)	Male/female		Age (years)		NYHA (I, II, III, IV)		Intervention		Duration (week)	Outcomes
		E	C	E	C	E	C	E	C		
Wang et al. 2020 [52]	40/40	26/14	24/16	68.63 ± 4.57	68.77 ± 7.16	0, 14, 18, 8	0, 13, 18, 9	QLQX + CAM	CAM	4	①②③
Wang et al. 2020 [53]	45/41	30/15	27/14	54.4 ± 10.8	53.9 ± 11.3	0, 9, 29, 7	0, 8, 28, 5	QLQX + CAM	CAM	8	①②③④
Dong, 2021 [54]	30/30	24/6	22/8	53.53 ± 10.03	52.27 ± 8.76	–		QLQX + CAM	CAM	12	①②③④
Li, 2021 [55]	50/50	27/23	26/24	65.12 ± 4.18	64.78 ± 4.68	0, 15, 22, 13	0, 16, 20, 14	QLQX + CAM	CAM	24	①②③④⑤
Zhang, 2022 [56]	40/40	–		–		–		QLQX + CAM	CAM	12	①②③④
Tan et al. 2022 [57]	42/41	22/20	21/20	68.42 ± 10.30	67.56 ± 6.83	–		QLQX + CAM	CAM	12	①②③
Wang et al. 2022 [58]	40/40	28/12	27/13	58.23 ± 11.22	59.90 ± 12.03	0, 19, 15, 6	0, 19, 16, 5	QLQX + CAM	CAM	12	①②③④
Wu et al. 2022 [59]	46/46	25/21	26/20	39.41 ± 6.37	38.56 ± 6.26	0, 16, 27, 3	0, 17, 25, 4	QLQX + CAM	CAM	12	①②③
Pan, 2022 [60]	43/43	22/21	23/20	59.78 ± 2.32	59.89 ± 2.24	0, 19, 17, 7	0, 18, 16, 9	QLQX + CAM	CAM	12	①②⑥
Yan et al. 2023 [61]	30/30	17/13	18/12	–		–		QLQX + CAM	CAM	12	①②③⑤
Han et al. 2023 [62]	39/39	18/21	16/23	43.33 ± 3.92	43.26 ± 3.85	0, 15, 12, 12	0, 16, 14, 9	QLQX + CAM	CAM	4	①②③④
Zhang et al. 2023 [63]	60/60	31/29	32/28	74.51 ± 4.67	74.74 ± 4.81	0, 27, 21, 12	0, 25, 22, 13	QLQX + CAM	CAM	16	①②⑥
Liu, 2023 [64]	44/44	30/14	32/12	64.78 ± 8.46	65.32 ± 8.25	0, 18, 17, 9	0, 15, 20, 9	QLQX + CAM	CAM	12	②
Luo et al. 2006 [65]	40/46	–		–		–		WX + CAM	CAM	2	①
Cui et al. 2009 [66]	28/32	35/25		48 ± 6		–		WX + CAM	CAM	12	②④
Zhao et al. 2009 [67]	84/84	43/41	40/44	–		–		WX + CAM	CAM	4	①
Wu et al. 2010 [68]	22/23	28/17		35 ± 5.5		–		WX + CAM	CAM	12	②④
Liu, 2012 [69]	50/50	25/25	24/26	–		–		WX + CAM	CAM	2	①
Feng, 2013 [70]	32/32	20/12	21/11	49.6 ± 5.3	50.4 ± 5.9	0, 7, 25, 0	0, 7, 25, 0	WX + CAM	CAM	4	①②
Wang, 2014 [71]	28/28	16/12	18/10	52.4 ± 4.31		–		WX + CAM	CAM	4	①
Wang, 2017 [72]	50/50	27/23	24/26	45.5 ± 5.7	44.8 ± 4.9	–		WX + CAM	CAM	4	①
Li et al. 2019 [73]	23/23	14/9	7/16	50.17 ± 10.20	50.83 ± 10.18	0, 0, 15, 8	0, 0, 16, 7	WX + CAM	CAM	12	①②④
He et al. 2019 [74]	30/30	21/9	20/10	52.97 ± 6.98	52.81 ± 6.27	0, 5, 11, 14	0, 5, 10, 15	WX + CAM	CAM	12	①②③
Tan et al. 2021 [75]	68/68	37/31	35/33	60.7 ± 0.2	60.6 ± 0.3	0, 7, 21, 40	0, 8, 21, 39	WX + CAM	CAM	12	①②③④
Ding, 2006 [76]	89/30	48/41	18/12	–		0, 4, 48, 37	0, 2, 16, 12	TXL + CAM	CAM	24	①②
Chen et al. 2019 [77]	43/43	20/23	22/21	65.1 ± 10.3	68.5 ± 9.2	0, 15, 19, 9	0, 13, 20, 10	TXL + CAM	CAM	8	①②④⑤⑥
Li et al. 2019 [78]	44/44	25/19	23/21	52.1 ± 6.5	51.2 ± 6.1	17, 17, 10, 0	14, 21, 9, 0	TXL + CAM	CAM	8	①②③⑤⑥
Liang et al. 2020 [79]	73/73	43/30	46/27	53.3 ± 5.7	53.3 ± 5.7	35, 27, 11, 0	36, 27, 10, 0	TXL + CAM	CAM	8	①②③
Li et al. 2020 [80]	56/56	36/20	35/21	62.73 ± 14.15	61.96 ± 13.88	0, 21, 23, 12	0, 20, 25, 11	TXL + CAM	CAM	12	①②③⑤
Cao, 2020 [81]	42/42	19/23	20/22	47.08 ± 3.53	46.92 ± 3.33	0, 16, 20, 6	0, 17, 20, 5	TXL + CAM	CAM	8	②③⑤⑥
Zhou et al. 2021 [82]	48/48	25/23	27/21	46.70 ± 6.19	45.90 ± 5.93	17, 19, 12, 0	18, 20, 10, 0	TXL + CAM	CAM	1	①②
Zhu, 2021 [83]	42/42	24/18	25/17	54.52 ± 4.78	55.02 ± 4.93	–		TXL + CAM	CAM	12	①②③
He et al. 2011 [84]	28/25	20/8	15/10	60 ± 18	58 ± 16	–		QSYQ + CAM	CAM	48	①②③

Table 2 (continued)

Study ID	*N* (E/C)	Male/female		Age (years)		NYHA (I, II, III, IV)		Intervention		Duration (week)	Outcomes
		E	C	E	C	E	C	E	C		
Wang et al. 2013 [85]	60/60	72/48		67.5 ± 5.5		–		QSYQ + CAM	CAM	6	①
Wang, 2007 [86]	30/20	18/12	12/8	41 ± 15	39.5 ± 13.5	0, 12, 13, 5	0, 8, 10, 2	SXBX + CAM	CAM	4	①③
Deng et al. 2013 [87]	65/67	76/56		62 ± 11		–		SXBX + CAM	CAM	12	②⑤
Ma et al. 2018 [88]	30/30	17/13	17/13	35.41 ± 13.02	34.51 ± 10.32	0, 16, 14, 0	0, 14, 16, 0	SXBX + CAM	CAM	8	①②④⑥
Qian et al. 2012 [89]	56/56	64/48		63 ± 17				YXST + CAM	CAM	12	①②③
Fu et al. 2014 [90]	64/62	42/22	40/22	65 ± 10.2	64 ± 10.8	0, 0, 48, 16	0, 0, 46, 16	YXST + CAM	CAM	12	①②
Wang et al. 2013 [91]	60/60	37/23	38/22	52.34 ± 9.18	51.52 ± 10.20	–		YXSC + CAM	CAM	12	①②④
Jiang, 2013 [92]	30/30	21/9	20/10	40 ± 12	41 ± 11	0, 14, 13, 3	0, 15, 12, 3	YXSC + CAM	CAM	12	①②③④
Cen et al. 2020 [93]	45/45	24/21	23/22	54.9 ± 10.2	53.9 ± 10.2	0, 0, 26, 19	0, 0, 25, 20	GTTL + CAM	CAM	8	①②③⑥
Wang, 2022 [94]	35/35	20/15	19/16	56.99 ± 5.33	57.69 ± 5.32	0, 17, 18, 0	0, 19, 16, 0	GTTL + CAM	CAM	24	①②③

Age is expressed as mean ± standard deviation

① clinical effectiveness rate (CER), ② left ventricular ejection fraction (LVEF), ③ left ventricular end-diastolic dimension (LVEDD), ④ six-min walk test (6MWT), ⑤ brain natriuretic peptide (BNP), and ⑥ cardiac output (CO)

E experimental group, *C* control group, *QLQX* Qili Qiangxin capsule, *WX* Wenxin granule, *TXL* Tongxinluo capsule, *QSYQ* Qishen Yiqi dropping pill, *SXBX* Shexiang Baoxin pill, *YXST* Yangxinshi tablet, *YXSC* Yixinshu capsule, *GTTL* Getong Tongluo capsule, *CAM* complementary and alternative medicine

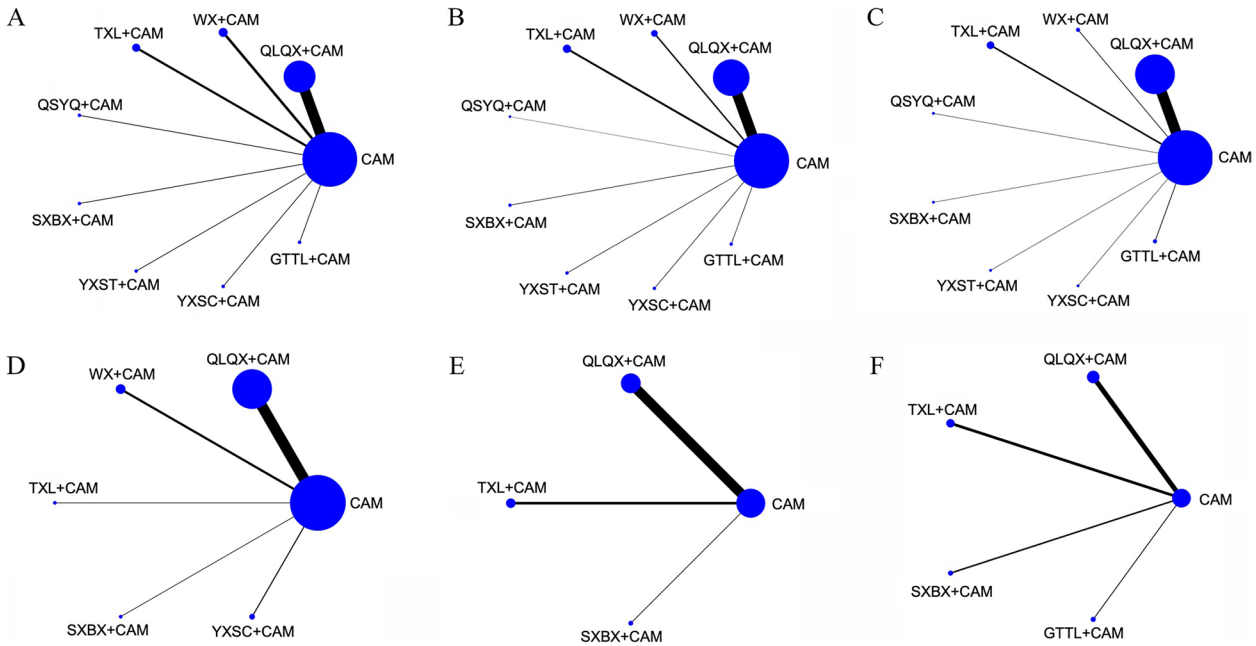

Fig. 2 Network graph of the outcomes. **A** Clinical effectiveness rate (CER). **B** Left ventricular ejection fraction (LVEF). **C** Left ventricular end-diastolic dimension (LVEDD). **D** Six-minute walk test (6MWT). **E** Brain natriuretic peptide (BNP). **F** Cardiac output (CO). *Abbreviations*: QLQX, Qili Qiangxin capsule; WX, Wenxin granule; TXL, Tongxinluo capsule; QSYQ, Qishen Yiqi dropping pill; SXBX, Shexiang Baoxin pill; YXST, Yangxinshi tablet; YXSC, Yixinshu capsule; GTTL, Getong Tongluo capsule; CAM, complementary and alternative medicine

and double chromosphere method were also used for randomization [35, 59, 61, 87]. Seven studies used randomization methods prone to high risk of bias including grouping by the time of admission, odd and even outpatient numbers, and visiting sequence [40, 68, 70, 73, 86, 90, 91]. The remaining RCTs referred to only random grouping. One study described the information on allocation concealment which was grouped using the sealed envelope method [58] and one study was designed as a double-blind study [35]. Additionally, the rest of the studies did not provide detailed information on allocation concealment and blinding. The detection bias was evaluated as "low risk" because the measurement of related results of the included RCTs was not affected by the blinding toward the outcome assessors. All the study outcome reports were complete; therefore, it was considered that there was no risk of incomplete outcome data. Considering that the complete implementation scheme could not be acquired,

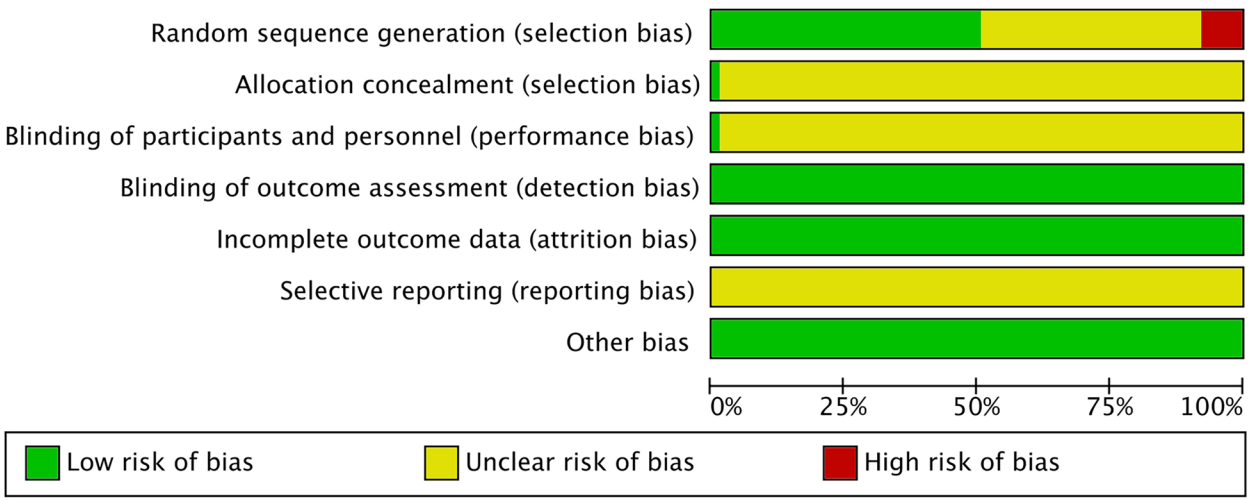

Fig. 3 Risk-of-bias graph

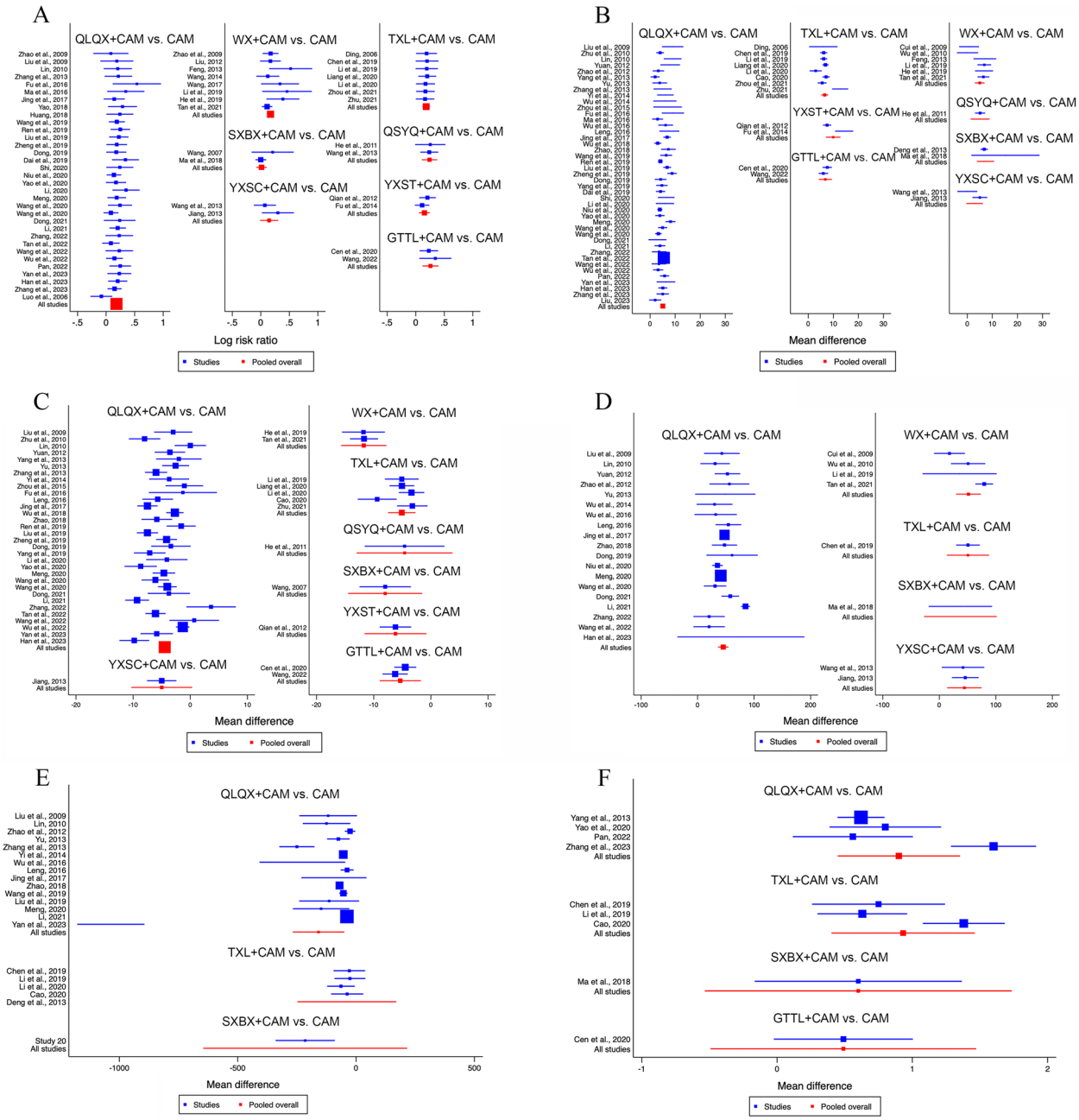

Fig. 4 Forest plot of the outcomes. **A** Clinical effectiveness rate (CER). **B** Left ventricular ejection fraction (LVEF). **C** Left ventricular end-diastolic dimension (LVEDD). **D** Six-minute walk test (6MWT). **E** Brain natriuretic peptide (BNP). **F** Cardiac output (CO). *Abbreviations*: QLQX, Qili Qiangxin capsule; WX, Wenxin granule; TXL, Tongxinluo capsule; QSYQ, Qishen Yiqi dropping pill; SXBX, Shexiang Baoxin pill; YXST, Yangxinshi tablet; YXSC, Yixinshu capsule; GTTL, Getong Tongluo capsule; CAM, complementary and alternative medicine

the reporting bias was evaluated as "unclear risk." No other obvious bias was observed in all included studies, so this review assumed that there were no other bias risks. The quality assessment of the included RCTs is shown in Fig. 3.

Outcomes

CER

Fifty-eight RCTs reported the CER of eight types of CPMs. Figure 4A and Table 3 showed that in GTTL+CAM vs CAM (OR = 5.95, 95% CI 2.04–17.40), QSYQ+CAM vs CAM (OR = 5.82, 95% CI 2.08–16.28), YXST+CAM

Table 3 Risk ratios/mean difference (95%CIs) of the CER and LVEF

CER (left lower part)				LVEF (right upper part)				
GTTL + CAM	−1.70 (−6.30, 2.91)	−1.71 (−4.41, 0.98)	−0.25 (−3.20, 2.70)	−1.83 (−5.08, 1.42)	−3.90 (−8.13, 0.32)	−3.13 (−7.04, 0.77)	−0.46 (−4.77, 3.85)	**−6.80 (−9.42, −4.18)**
1.02 (0.23, 4.52)	**QSYQ + CAM**	−0.02 (−3.86, 3.82)	−1.45 (−5.47, 2.58)	−0.14 (−4.39, 4.11)	−2.21 (−7.24, 2.82)	−4.83 (−9.60, −0.06)	−2.15 (−7.26, 2.95)	**−5.10 (−8.89, −1.31)**
1.69 (0.56, 5.07)	1.65 (0.58, 4.75)	**QLQX + CAM**	−1.47 (−2.96, 0.03)	−0.12 (−2.14, 1.91)	−2.19 (−5.56, 1.18)	−4.85 (−7.81, −1.89)	−2.17 (−5.64, 1.30)	**−5.08 (−5.70, −4.46)**
1.60 (0.50, 5.14)	1.56 (0.51, 4.83)	0.95 (0.56, 1.59)	**TXL + CAM**	−1.58 (−3.94, 0.78)	−3.66 (−7.24, −0.07)	−3.38 (−6.58, −0.18)	−0.71 (−4.38, 2.97)	**−6.55 (−7.91, −5.19)**
1.73 (0.55, 5.45)	1.69 (0.56, 5.12)	1.02 (0.63, 1.65)	1.08 (0.58, 2.01)	**WX + CAM**	−2.07 (−5.90, 1.76)	−4.97 (−8.46, −1.47)	−2.29 (−6.22, 1.64)	**−4.96 (−6.89, −3.04)**
3.07 (0.83, 11.37)	3.00 (0.84, 10.73)	1.81 (0.82, 4.00)	1.92 (0.79, 4.65)	1.78 (0.75, 4.20)	**YXSC + CAM**	−7.04 (−11.45, −2.63)	−4.36 (−9.13, 0.40)	−2.89 (−6.20, 0.42)
1.44 (0.34, 6.08)	1.41 (0.35, 5.75)	0.85 (0.32, 2.29)	0.90 (0.31, 2.62)	0.84 (0.29, 2.38)	0.47 (0.14, 1.59)	**YXST + CAM**	−2.67 (−7.14, 1.79)	**−9.93 (−12.83, −7.03)**
3.15 (0.65, 15.39)	3.08 (0.65, 14.61)	1.87 (0.57, 6.14)	1.97 (0.56, 6.93)	1.83 (0.53, 6.31)	1.03 (0.26, 4.13)	2.18 (0.48, 9.89)	**SXBX + CAM**	**−7.25 (−10.67, −3.84)**
5.95 (2.04, 17.40)	**5.82 (2.08, 16.28)**	**3.52 (2.78, 4.46)**	**3.73 (2.34, 5.92)**	**3.45 (2.27, 5.23)**	1.94 (0.91, 4.13)	**4.13 (1.58, 10.75)**	1.89 (0.59, 6.07)	**CAM**

The numbers in bold in the table indicate that there are statistically significant differences between this group and the CAM group

CER clinical effectiveness rate, *LVEF* left ventricular ejection fraction, *QLQX* Qili Qiangxin capsule, *WX* Wenxin granule, *TXL* Tongxinluo capsule, *QSYQ* Qishen Yiqi dropping pill, *SXBX* Shexiang Baoxin pill, *YXST* Yangxinshi tablet, *YXSC* Yixinshu capsule; *GTTL* Getong Tongluo capsule, *CAM* complementary and alternative medicine

Table 4 Surface under the cumulative ranking curve results of the outcomes

Intervention	CER	LVEF	LVEDD	6MWT	BNP	CO
QLQX + CAM	56%	39.5%	37.3%	56.6%	74.5%	72.6%
WX + CAM	54.1%	39.3%	95.9%	70.8%	–	–
TXL + CAM	60.2%	67.6%	47.3%	66.8%	34.5%	75.4%
QSYQ + CAM	80.2%	44.1%	42.6%	–	–	–
SXBX + CAM	26.8%	73.7%	71.2%	47.9%	73.6%	50.4%
YXST + CAM	65.2%	97.2%	58.3%	–	–	–
YXSC + CAM	23.7%	18.8%	45.2%	55.3%	–	–
GTTL + CAM	81.3%	69.3%	49.8%	–	–	43.4%
CAM	.2.4%	0.6%	2.4%	2.7%	17.5%	26.4%

QLQX Qili Qiangxin capsule, *WX* Wenxin granule, *TXL* Tongxinluo capsule, *QSYQ* Qishen Yiqi dropping pill, *SXBX* Shexiang Baoxin pill, *YXST* Yangxinshi tablet, *YXSC* Yixinshu capsule, *GTTL* Getong Tongluo capsule, *CAM* complementary and alternative medicine, *CER* clinical effectiveness rate, *LVEF* left ventricular ejection fraction, *LVEDD* left ventricular end-diastolic dimension, *6MWT* six-min walk test, *BNP* brain natriuretic peptide, *CO* cardiac output

vs CAM (OR = 4.13, 95% CI 1.58–10.75), TXL+CAM vs CAM (OR = 3.73, 95% CI 2.34–5.92), QLQX+CAM vs CAM (OR = 3.52, 95% CI 2.78–4.46), WX+CAM vs CAM (OR = 3.45, 95% CI 2.27–5.23), YXSC+CAM vs CAM (OR = 1.94, 95% CI 0.91–4.13), and SXBX+CAM vs CAM (OR =1.89, 95% CI 0.59–6.07), it was observed that the CPMs (GTTL, QSYQ, YXST, TXL, QLQX, and WX) combined with CAM had a better clinical effectiveness rate compared with CAM alone.

The results of SUCRA suggested that GTTL + CAM was the optimal combination, followed by QSYQ + CAM, YXST + CAM, and TXL + CAM (Table 4 and Fig. 5A).

LVEF

Sixty-six RCTs reported the LVEF of eight types of CPMs. As shown in Fig. 4B and Table 3, YXST + CAM vs CAM (MD = −9.93, 95% CI −12.83 to −7.03), SXBX + CAM vs CAM (MD = −7.25, 95% CI −10.67 to −3.84), GTTL + CAM vs CAM (MD = −6.80, 95% CI −9.42 to −4.18), TXL + CAM vs CAM (MD = −6.55, 95% CI −7.91 to −5.19), QSYQ + CAM vs CAM (MD = −5.10, 95% CI −8.89 to −1.31), QLQX + CAM vs CAM (MD = −5.08, 95% CI −5.70 to −4.46), and WX + CAM vs CAM (MD = −4.96, 95% CI −6.89 to −3.04) were more efficacious in improving LVEF compared with CAM alone, while the YXSC + CAM vs CAM (MD = −2.89, 95% CI −6.20 to 0.42) compared with CAM alone had no statistical significance.

YXST + CAM had the highest probability of being the best treatment on account of the enhancement of LVEF, and SXBX + CAM was the second most favorable intervention based on the SUCRA values (Table 4 and Fig. 5B).

LVEDD

Forty-five RCTs involving eight types of CPMs reported the LVEDD. As shown in Fig. 4C and Table 5, only WX + CAM vs CAM (MD = −11.7, 95% CI −15.70 to −7.79), SXBX + CAM vs CAM (MD = −8.00, 95% CI −14.47 to −1.53), YXST + CAM vs CAM (MD = −6.20, 95% CI −11.61 to −0.79), GTTL + CAM vs CAM (MD = −5.358, 95% CI −8.96 to −1.75), TXL + CAM vs CAM (MD = −5.10, 95% CI −7.50 to −2.69), and QLQX + CAM vs CAM (MD = −4.48, 95% CI −5.44 to −3.52) were more available in decreasing LVEDD compared with CAM alone, while no significant difference was observed for YXSC + CAM vs CAM and QSYQ + CAM vs CAM.

According to the SUCRA values, WX + CAM had the highest likelihood of being the best treatment for decreasing LVEDD, followed by SXBX + CAM and YXST + CAM (Table 4 and Fig. 5C).

6MWT

Twenty-seven RCTs involving five CPMs (QLQX, WX, TXL, SXBX, and YXSC) reported the 6MWT. Figure 4D and Table 5 show that WX + CAM vs CAM (MD = −51.58, 95% CI −73.40 to −29.76), TXL + CAM vs CAM (MD = −50.73, 95% CI −88.24 to −13.22), QLQX + CAM vs CAM (MD = −45.3, 95% CI −54.59 to −36.17), and YXSC + CAM vs CAM (MD = −44.44, 95% CI −74.91 to −13.96) were more effective in improving 6MWT compared with CAM alone. However, SXBX + CAM vs CAM (MD = −37.32, 95% CI −101.49 to 26.85) compared with CAM alone had no statistical significance.

As shown in Table 4 and Fig. 5D, the SUCRA values affirmed that WX + CAM had the highest likelihood of being the best treatment for improving 6MWT, followed by TXL + CAM and QLQX + CAM.

BNP

Twenty RCTs involving three CPMs (QLQX, TXL, SXBX, and XML) assessed the BNP. Figure 4E and Table 6 show that only QLQX + CAM (MD = −158.59, 95% CI −267.70 to −49.49) was more effective in decreasing

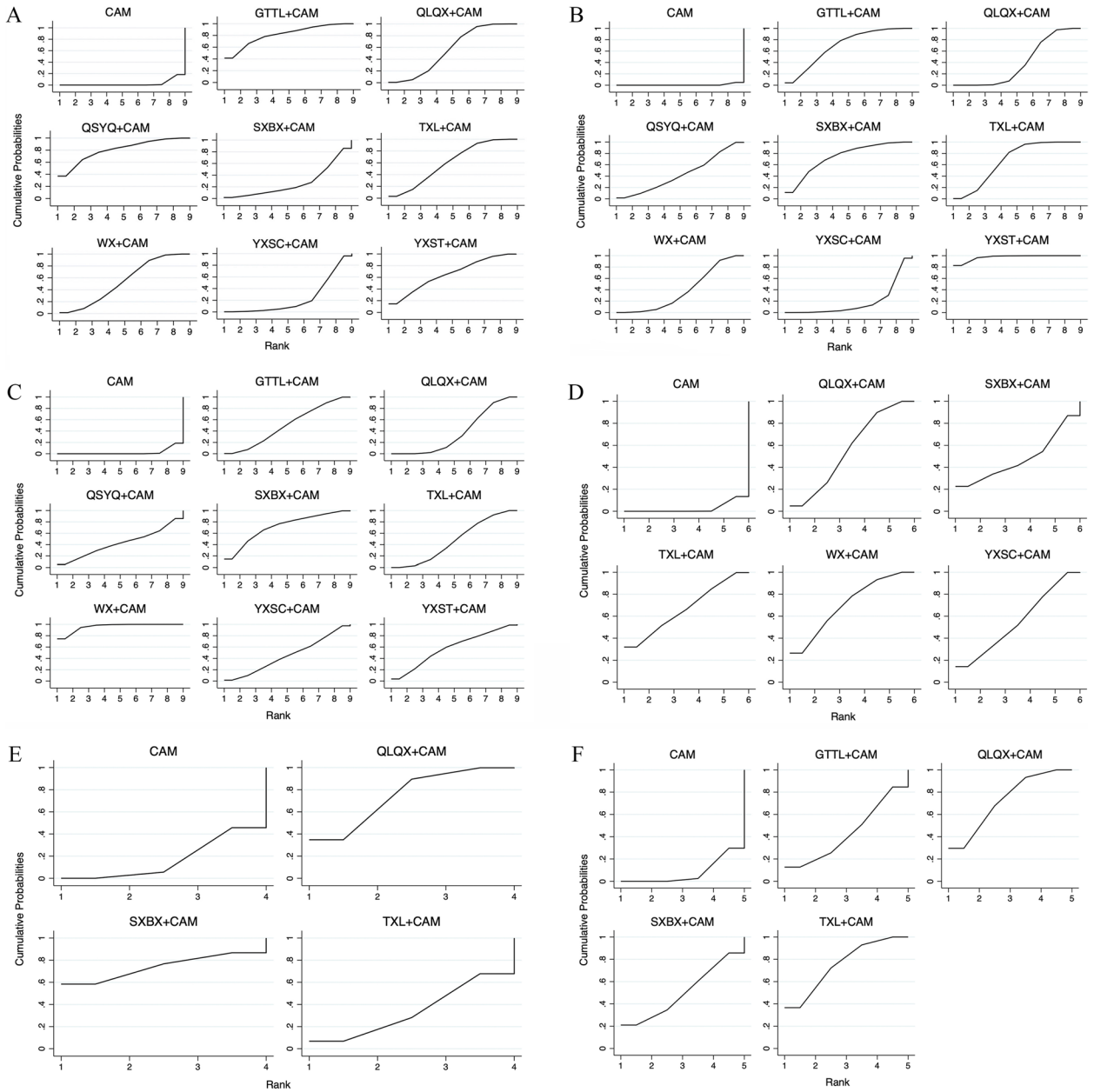

Fig. 5 Plot of the surface under the cumulative ranking curves for outcomes. **A** Clinical effectiveness rate (CER). **B** Left ventricular ejection fraction (LVEF). **C** Left ventricular end-diastolic dimension (LVEDD). **D** Six-minute walk test (6MWT). **E** Brain natriuretic peptide (BNP). **F** Cardiac output (CO). *Abbreviations*: QLQX, Qili Qiangxin capsule; WX, Wenxin granule; TXL, Tongxinluo capsule; QSYQ, Qishen Yiqi dropping pill; SXBX, Shexiang Baoxin pill; YXST, Yangxinshi tablet; YXSC, Yixinshu capsule; GTTL, Getong Tongluo capsule; CAM, complementary and alternative medicine

BNP compared with CAM alone, while no significant difference was observed for TXL + CAM vs CAM and SXBX + CAM vs CAM. Similarly, the SUCRA values suggested that QLQX + CAM had the highest likelihood of being the best intervention for the reduction in BNP (Table 4 and Fig. 5E).

CO

Nine RCTs involving four CPMs (QLQX, TXL, SXBX, and GTTL) reported changes in the CO level before and after therapy. Figure 4F and Table 6 indicated that only TXL + CAM (MD = −0.93, 95% CI −1.46 to −0.40) and QLQX + CAM (MD = −0.90, 95% CI −1.35 to −0.45) effectively increased CO level compared with CAM

Table 5 Mean difference (95%CIs) of the LVEDD and 6 MWT

LVEDD (left lower part)				**6 MWT (right upper part)**				
WX + CAM	− 14.26 (− 82.04, 53.52)	–	–	− 0.85 (− 44.25, 42.55)	− 7.15 (− 44.61, 30.32)	–	− 6.20 (− 29.81, 17.41)	**− 51.58 (− 73.40, − 29.76)**
− 3.74 (− 11.33, 3.84)	**SXBX + CAM**	–	–	− 13.41 (− 87.74, 60.92)	− 7.12 (− 78.16, 63.92)		− 8.06 (− 72.89, 56.77)	− 37.32 (− 101.49, 26.85)
− 5.54 (− 12.24, 1.16)	− 1.80 (− 10.24, 6.64)	**YXST + CAM**	–	–	–	–	–	–
− 6.39 (− 11.74, − 1.04)	− 2.65 (− 10.05, 4.76)	− 0.85 (− 7.35, 5.66)	**GTTL + CAM**	–	–	–	–	–
− 6.64 (− 11.27, − 2.02)	− 2.90 (− 9.81, 4.00)	− 1.10 (− 7.02, 4.82)	− 0.26 (− 4.59, 4.08)	**TXL + CAM**	− 6.29 (− 54.62, 42.03)		− 5.35 (− 43.97, 33.28)	**− 50.73 (− 88.24, − 13.22)**
− 6.74 (− 13.37, − 0.11)	− 3.00 (− 11.38, 5.38)	− 1.20 (− 8.79, 6.39)	− 0.35 (− 6.78, 6.07)	− 0.10 (− 5.94, 5.74)	**YXSC + CAM**	–	− 0.95 (− 32.77, 30.88)	**− 44.44 (− 74.91, − 13.96)**
− 7.14 (− 16.41, 2.13)	− 3.40 (− 13.99, 7.19)	− 1.60 (− 11.58, 8.38)	− 0.75 (− 9.88, 8.37)	− 0.50 (− 9.22, 8.22)	− 0.40 (− 10.33, 9.53)	**QSYQ + CAM**	–	–
− 7.26 (− 11.33, − 3.19)	− 3.52 (− 10.06, 3.03)	− 1.72 (− 7.21, 3.78)	− 0.87 (− 4.60, 2.86)	− 0.62 (− 3.21, 1.98)	− 0.52 (− 5.93, 4.89)	− 0.12 (− 8.56, 8.32)	**QLQX + CAM**	**− 45.38 (− 54.59, − 36.17)**
− 11.74 (− 15.70, − 7.79)	**− 8.00 (− 14.47, − 1.53)**	**− 6.20 (− 11.61, − 0.79)**	**− 5.35 (− 8.96, − 1.75)**	**− 5.10 (− 7.50, − 2.69)**	− 5.00 (− 10.32, 0.32)	− 4.60 (− 12.99, 3.79)	**− 4.48 (− 5.44, − 3.52)**	**CAM**

The numbers in bold in the table indicate that there are statistically significant differences between this group and the CAM group

LVEDD left ventricular end-diastolic dimension, *6MWT* six-min walk test, *QLQX* Qili Qiangxin capsule, *WX* Wenxin granule, *TXL* Tongxinluo capsule, *QSYQ* Qishen Yiqi dropping pill, *SXBX* Shexiang Baoxin pill, *YXST* Yangxinshi tablet, *YXSC* Yixinshu capsule; *GTTL* Getong Tongluo capsule, *CAM* complementary and alternative medicine

Table 6 Mean difference (95%CIs) of the BNP and CO

BNP (left lower part)		CO (right upper part)		
TXL + CAM	−0.03 (−0.73, 0.66)	−0.33 (−1.58, 0.92)	−0.44 (−1.56, 0.67)	**−0.93 (−1.46, −0.40)**
119.44 (−115.88, 354.76)	**QLQX + CAM**	−0.30 (−1.52, 0.92)	−0.41 (−1.49, 0.67)	**−0.90 (−1.35, −0.45)**
175.85 (−302.52, 654.21)	56.41 (−387.74, 500.56)	**SXBX + CAM**	−0.11 (−1.61, 1.39)	−0.60 (−1.73, 0.53)
–	–	–	**GTTL + CAM**	−0.49 (−1.47, 0.49)
−39.15 (−247.65, 169.34)	**−158.59 (−267.70, −49.49)**	−215.00 (−645.54, 215.54)	–	**CAM**

The numbers in bold in the table indicate that there are statistically significant differences between this group and the CAM group

BNP brain natriuretic peptide, *CO* cardiac output, *QLQX* Qili Qiangxin capsule, *TXL* Tongxinluo capsule, *SXBX* Shexiang Baoxin pill, *GTTL* Getong Tongluo capsule, *CAM* complementary and alternative medicine

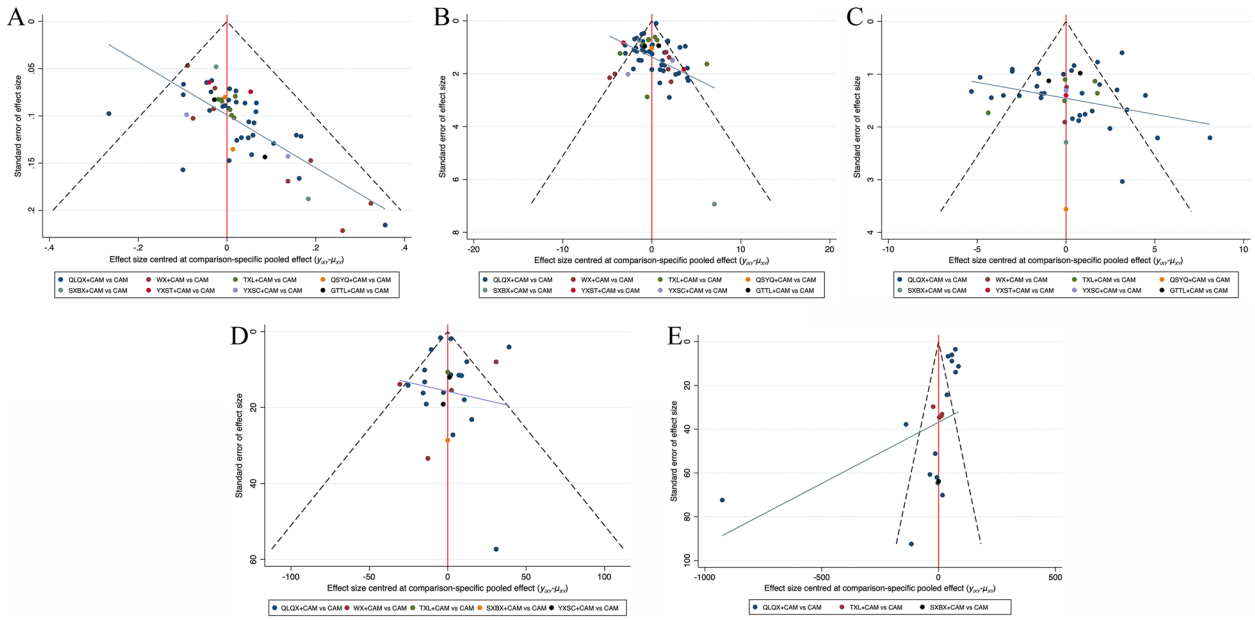

Fig. 6 Funnel plots of the CER, LVEF, LVEDD, 6MWT, and BNP. **A** Clinical effectiveness rate (CER). **B** Left ventricular ejection fraction (LVEF). **C** Left ventricular end-diastolic dimension (LVEDD). **D** Six-minute walk test (6MWT). **E** Brain natriuretic peptide (BNP). QLQX, Qili Qiangxin capsule; WX, Wenxin granule; TXL, Tongxinluo capsule; QSYQ, Qishen Yiqi dropping pill; SXBX, Shexiang Baoxin pill; YXST, Yangxinshi tablet; YXSC, Yixinshu capsule; GTTL, Getong Tongluo capsule; CAM, complementary and alternative medicine

alone, while no significant difference was observed for SXBX + CAM vs CAM and GTTL + CAM vs CAM.

The SUCRA values suggested that TXL + CAM could be the optimal choice for increasing CO levels in DCM-HF patients, followed by QLQX + CAM (Table 4 and Fig. 5F).

Safety

Regarding safety, 38 RCTs provided detailed information on the conditions (Additional file 1: Table S2). These studies reported that there were no serious treatment-emergent adverse events. Mild treatment-emergent adverse events such as cough, nausea, vomiting, dizziness, sleepiness, and arrhythmia were reported in 36 RCTs, revealing no significant impact on the study. The remaining two studies [65, 68] only reported whether treatment-emergent adverse events occurred but no further details were available.

Publication bias

Since the number of RCT studies reporting the CER, LVEF, LVEDD, 6MWT, and BNP was more than 10, the publication bias of these five outcomes was examined d using funnel plots (Fig. 6). Points with different colors represent different comparisons between interventions. We found that the funnel plots of these outcomes were not visually symmetrical, showing potential publication bias or a small sample effect; moreover, the lack of negative results might have also contributed to the bias.

Table 7 GRADE assessment for the outcomes

Outcome	Number	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
CER	58	RCT	Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate
LVEF	66	RCT	Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate
LVEDD	45	RCT	Serious	Serious	Not serious	Not serious	None	⊕⊕◯◯ Low
6MWT	27	RCT	Serious	Not serious	Not serious	Serious	None	⊕⊕◯◯ Low
BNP	20	RCT	Serious	Not serious	Not serious	Serious	None	⊕⊕◯◯ Low
CO	9	RCT	Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate

CER clinical effectiveness rate, *LVEF* left ventricular ejection fraction, *LVEDD* left ventricular end-diastolic dimension, *6MWT* six-min walk test, *BNP* brain natriuretic peptide, *CO* cardiac output

GRADE assessment

As shown in Table 7, a summary of the evidence grade evaluation of the included outcomes was performed using the GRADE method. The findings supported that the evidence was graded from low to moderate. The risk of bias was the most important factor in evidence degradation, followed by imprecision and inconsistency. Randomization, allocation concealment, and blinding were common biases in the included studies, suggesting improvements in the design of future studies on the treatment of DCM-HF with CPMs.

Discussion

This NMA included 77 RCTs, involving 6980 participants, with 8 CPMs identified for the treatment of DCM-HF, including QLQX, WX, TXL, QSYQ, SXBX, YXST, YXSC, and GTTL. Integrating NMA results and ranking analysis, it was observed that the combination of the aforementioned eight CPMs with CAM could not only enhance the treatment efficacy but also had a positive effect on improving LVEF, LVEDD, 6MWT, BNP, and CO compared with CAM alone. Concerning the enhancement of LVEF, YXST + CAM had the highest probability of being the best treatment. With regard to the improvement in LVEDD and 6MWT, WX + CAM had the highest likelihood of being the best intervention. In terms of the reduction in BNP, QLQX + CAM might be the optimal choice. On account of increasing CO levels, TXL + CAM had the highest likelihood of being the best intervention. Moreover, no serious treatment-emergent adverse events were recorded among all eligible studies. The GRADE assessment, however, found moderate certainty evidence for CER, LVEF, and CO only, and low for all other outcomes. We relatively determined that the aforementioned eight CPMs combined with CAM could play a positive role in improving the CER, LVEF, and CO of patients compared with CAM alone. Whether CPMs combined with CAM could improve LVEDD, 6MWT, and BNP remained uncertain considering the low grade of evidence certainty. However, we were inclined to believe that the combination of CPMs and CAM could improve LVEDD, 6MWT, and BNP to some extent because it was relatively obvious that CPMs combined with CAM could increase CER among these individuals which was primarily based on NYHA. In brief, it is advisable that we refer to these results with caution.

Briefly speaking, QLQX + CAM, TXL + CAM, WX + CAM, and YXST + CAM showed a preferable improvement in patients with DCM-HF when unified considering the clinical effectiveness rate and other outcomes. Nevertheless, given the special characteristics of different types of CPMs, the patient's condition should also be taken into account when making clinical decisions to make the best use of CPMs in the treatment of DCM-HF. QLQX was an oral traditional CPM composed of 10 kinds of Chinese herbal medicine, which had the functions of replenishing qi and warming yang, activating blood, and excreting water. The efficacy of QLQX against cardiac hypertrophy and remodeling has been demonstrated in substantial studies. Data from a multicenter double-blind RCT [95] of 512 subjects screened from 32 sites in China proposed that QLQX demonstrated superior performance in comparison to the CAM alone with respect to NYHA functional classification, LVEF, 6MWT, and quality of life. Experiments [96] implied that QLQX had significantly positive effects on inhibiting myocardial inflammation, promoting cardiomyocyte proliferation, and improving histopathologic changes, leading to improved cardiac remodeling and cardiac function. Further pharmacological study [97] showed that one possible mechanism underlying the cardioprotective effects of QLQX may involve the regulation of alleviating apoptotic and autophagic cell death through inhibition of the ROS/AMPK/mTOR signaling pathway. TXL, based on a treatment method of tonifying qi and activating blood in the sense of traditional Chinese medicine theory, was mainly composed of 12 kinds of Chinese herbal medicine. Two

meta-analyses [98] involving a total of 2940 subjects showed that the addition of TXL to current CAM treatment may possibly lower the risk of adverse cardiovascular events such as restenosis, recurrent myocardial reinfarction, recurrent angina pectoris, and mortality. Data from the China Tongxinluo Study for myocardial protection in patients with Acute Myocardial Infarction (CTS-AMI) [99] which enrolled 3777 patients from 124 hospitals in China supported that TXL, as an adjunctive therapy in addition to guideline-directed treatments, significantly improved both 30-day and 1-year clinical outcomes in patients with ST-segment elevation myocardial infarction. Additionally, pharmacological research revealed that TXL could benefit the cardiovascular system potentially through multiple mechanisms including anti-inflammation [100], regulation of lipid metabolism [101], the cardiovascular endothelial protective effect [102], protection against ischemia–reperfusion injury [103], and prevention of myocardial fibrosis [104]. TXL also played a positive role in inhibiting atherosclerosis development and stabilizing plaque [105], inhibiting apoptosis and promotion of autophagy [106], and ameliorating vascular remodeling [107].

WX was the first Chinese anti-arrhythmic medicine to be approved by the China Food and Drug Administration and has been increasingly used as an alternative approach for cardiovascular diseases. WX appeared to be more effective in reducing the frequency of ventricular premature complexes, improving LVEF and 6MWT in patients with ventricular premature complexes and HF [108, 109]. The pharmacological effects of WX were closely related to its components. Thereinto, Dangshen (Codonopsis Radix), the dried root of *Codonopsis pilosula* (Franch.) Nannf., played a crucial role in maintaining the well-being of the Chinese population. A study [110] focused on its neuron-regeneration-enhancing properties by acting on the regulation of the cell cycle controlling proteins and signaling pathway regulators. Sanqi (Notoginseng Radix et Rhizoma), a valuable herb with obvious efficacy and favorable safety, has been used in clinical applications for hundreds of years. Substantial studies have confirmed that Sanqi (Notoginseng Radix et Rhizoma) had a positive effect on reducing inflammation [111], regulating lipid metabolism [112], regulating the coagulation system [113], inhibiting ischemia-induced cardiomyocyte apoptosis [114], preventing cardiac ischemic-reperfusion injury and improving energy metabolism of myocardial cells [115]. Gansong (Nardostachyos Radix et Rhizoma), the dried rhizome and root of *Nardostachys jatamansi* DC., could regulate qi and relieve pain, resolve depression, and invigorate the spleen. Previous studies have demonstrated that Gansong (Nardostachyos Radix et Rhizoma) exhibited cardioprotective effects by inhibiting myocardial apoptosis, inflammation, and oxidative stress [116–118]. YXST comprised 13 kinds of Chinese herbs with the clinical efficacy of replenishing qi and activating blood, resolving stasis, and relieving pain. It has been reported that YXST had cardio-protection effects on ischemia–reperfusion injury via the regulation of multiple metabolic pathways involving oxidative stress, energy metabolism, fatty acid, and amino acid metabolisms [119]. A network pharmacology-based study showed that the cardiovascular protective effect of YXST mainly involved the immune and cardiovascular systems [120]. YXST could also enhance cardiac function and exercise tolerance in HF, such as improving cardiac structure, decreasing myocardial oxygen consumption, and reducing myocardial infarct size [121]. Quantitative analysis [122] found that eleven compounds, including puerarin, daidzin, ferulic acid, calycosin-7-O-β-D-glucoside, tetrahydropalmatine, coptisine, epiberberine, jatrorrhizine, berberine, palmatine chloride, and icariin, were extracted based on the optimum extraction conditions.

In addition to efficacy, the safety of CPMs in the treatment of DCM-HF should be given enough attention. Nevertheless, only approximately half of the included studies provided information on treatment-emergent adverse events, and 39 RCTs did not specifically report the conditions of using CPMs, leading to insufficient robust evidence of drug safety in the treatment of DCM-HF. CPMs, especially the formula that comprises several herbs containing complex compounds at specific ratios and doses, have been used effectively as alternative and complementary therapies in cardiovascular diseases in China and many other Asian countries, with the characteristics of steady properties and little side-effect. Furthermore, it was the responsibility of clinicians to inform patients of any potential adverse reactions detailedly at the first opportunity when they received CPMs.

To our knowledge, this review was the first NMA to synthetically assess and rank the relative efficacy of the combination of CPMs with CAM against DCM-HF compared with CAM alone. The findings may potentially provide a reference for the clinical decision of treating DCM-HF with CPMs and contribute to the development of new treatment and management strategies for DCM-HF. Meanwhile, this review also objectively examined the certainty of each piece of evidence, which will help to guide the clinical application of CPMs in clinical decision-making.

Several limitations of this review need to be acknowledged. First, owing to the history of traditional Chinese medicine and the adoption of CPMs in places like Europe and the US, all of the included RCTs were conducted in China, resulting in reducing the

generalizability of the results. Second, the overall quality of the included RCTs was not high. Most of the included studies were single-center studies with short duration and small sample sizes. Only half of the RCTs described the methods of generating randomization, such as a random number table, draw method, block randomization, stratified randomization, touch ball method, and double chromosphere method, and only one study provided information on allocation concealment and another one mentioned blinding, leading to a decreased reliability of the evidence. Third, the reliability of the findings may have been influenced by the fact that no direct comparisons were performed between different CPMs and no closed loops formed between the studies according to the evidence network graph. Finally, we should pay attention to improving the methodological quality and design optimization for clinical trials. Information about the research plan should be reported in detail as possible, including population, diagnostic criteria, inclusion and exclusion criteria, interventions, duration of treatment, follow-up, statistical methods, etc.

Conclusion

The results of our NMA indicated that a combination of CPMs with CAM exerted a more positive effect in treating DCM-HF compared with CAM alone. QLQX + CAM, TXL + CAM, WX + CAM, and YXST + CAM showed a preferable improvement in patients with DCM-HF when unified considering the clinical effectiveness rate and other outcomes. Furthermore, given the special characteristics of different types of CPMs, the patient's condition should also be taken into account when making clinical decisions. Nevertheless, due to the limited information on CPMs for DCM-HF and the uneven distribution of studies among interventions, more high-quality research with a focus on the efficacy of CPMs for DCM-HF are required to provide more powerful evidence to confirm our findings.

Abbreviations

CPM	Chinese patent medicine
DCM	Dilated cardiomyopathy
HF	Heart failure
NMA	Network meta-analysis
RCT	Randomized controlled trial
QLQX	Qili Qiangxin capsule
WX	Wenxin granule
TXL	Tongxinluo capsule
QSYQ	Qishen Yiqi dropping pill
SXBX	Shexiang Baoxin pill
YXST	Yangxinshi tablet
YXSC	Yixinshu capsule
GTTL	Getong Tongluo capsule
CAM	Complementary and alternative medicine
CER	Clinical effectiveness rate
LVEF	Left ventricular ejection fraction
LVEDD	Left ventricular end-diastolic dimension
6MWT	Six-min walk test
BNP	Brain natriuretic peptide
CO	Cardiac output
NYHA	New York Heart Association
SUCRA	Surface under the cumulative ranking curve
MD	Mean difference
RR	Risk ratio
CI	Confidence interval

Supplementary Information

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Additional file 1: Table S1. PRISMA checklist for network meta-analysis. Table S2. Safety of the included studies.

Additional file 2. Search strategy.

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Authors' contributions

JL and ST contributed to the study concept and design. ST and LY conducted the meta-analysis, interpreted the data, and drafted the manuscript. ST, LY, MS, and DY were responsible for the literature search, data collection, and quality assessment. JW, TX, and XH contributed to the data collection and verification. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

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Availability of data and materials

The data used in this review were extracted from published studies, and the original data could be obtained by searching databases. Other data supporting the results of this review are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have consent for publication.

Competing interests

The authors declare that they have no competing interests.

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